DATE: March 31, 2000

MEMORANDUM

SUBJECT: **OXAMYL: TOXICOLOGY CHAPTER FOR RED**

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TO: Christina Jarvis
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PC Code No.: 103801
DP Barcode No.: D263844
Submission No.: S576382

ACTION REQUESTED: Revise toxicology chapter for the Oxamyl RED.

RESPONSE: The toxicology database for oxamyl has been reviewed by the Reregistration Branch 1I. The database has undergone QA/QC by the Toxicology Science Advisory Council (TOX SAC) on February 6, 1998 and peer reviewed by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) on June 8, 1999 and July 15, 1999 and by the HED FQPA Safety Factor Committee on August 30, 1999. There are no DATA GAPS. The toxicology database for oxamyl is adequate to support a Reregistration Eligibility Decision (RED). The toxicology chapter for the oxamyl has been revised as per phase 2 revisions memo of March 31, 2000 and the revised RED is included in the following pages:

OXAMYL: TOXICOLOGY CHAPTER FOR RED

DP Barcode No. D263844
Submission No. S576382
Tox. Chem. No. 561A

Reregistration Case No.0253
P.C. Code No. 103801

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OXAMYL: TOXICOLOGY CHAPTER FOR RED

I. TOXICOLOGY DATA BASE

HAZARD PROFILE

The toxicological data base on oxamyl is adequate to support reregistration eligibility. There are no DATA Gaps.

Oxamyl, ethanimidothioic acid, 2-(dimethylamino)-N-{[(methylamino)carbonyl]oxy}-2-oxo-, methyl ester; DPX-D1410-196; DPX-D1410-196 Technical; methyl 2-(dimethylamino)-N-{[(methylamino)carbonyl]oxy}-2-oxo-ethanimidothioate; methyl N',N'-dimethyl-N-[(methylcarbamoyl)oxy]-1-thiooxamimidate, is a water soluble carbamate insecticide (nematicide/acaricide) currently registered under terrestrial food and non-food category for use on field crops, vegetables, and fruits.

With the exception of the oral and inhalation LD_{50} studies (Category I & II, respectively), other acute studies have demonstrated oxamyl has low acute toxicity by other routes of administration (Category III & IV). Oxamyl is a mild eye irritant. It is not a skin sensitizer or a skin irritant in animal studies.

Generally, a NOAEL/LOAEL from the chronic study is selected for establishing the chronic RfD. However, for Oxamyl, the HIARC selected a NOAEL from an acute neurotoxicity study based on weight of the evidence of the toxicity data such as the chronic dog and rat studies which yielded a higher NOAEL/LOAEL compared to the acute neurotoxicity study. Further the measurement of ChEI was not conducted at the peak time in the chronic studies. Since the acute NOAEL (0.1 mg/kg) is protective of any maternal/developmental effects and chronic exposure (repeated), there is high confidence in the chronic RfD derived from the acute neurotoxicity study in rat.

Two acceptable 21-day dermal toxicity studies are available in the data base. Although in one study (MRID Nos. 40827601 & 41118201) lower NOAELs for ChEI were observed, this study was not used for risk assessment because of uncertainty regarding restraining of animals during the study. In the second study (MRID 44751201) no dermal toxicity was observed; however, systemic toxicity related to blood and brain ChEI was observed in females at 75 mg/kg dose level. The NOAEL in females was 50 mg/kg. There were no effects in males at doses up to and including 75 mg/kg.

No developmental toxicity was seen at the highest dose tested (4 mg/kg) following in utero exposure to rabbits. Following in utero exposure to rats, decreased fetal body weights were seen in the presence of maternal toxicity. In the two-generation reproduction study off-spring toxicity was seen only in the presence of parental/systemic toxicity at the highest dose tested (5.2 mg/kg). Therefore, there was no indication of increased susceptibility following exposure to Oxamyl.

In an acute neurotoxicity study in rats, neurobehavioral effects (FOB findings and numerous clinical signs) were observed at a dose level of 0.75 mg/kg/day (females) and 1 mg/kg/day (males). In the dietary subchronic neurotoxicity study the same types of findings were observed at higher doses; males (14.9 mg/kg) and females (19.9 mg/kg) with a NOAEL of 2.1 mg/kg (males) and 2.4 mg/kg (females). Neurotoxic effects were also seen in maternal animals in the rat developmental toxicity study and also seen in chronic dog studies. No neuropathological findings were associated with

neurotoxicity effects in the above mentioned studies, except retinal photoreceptor cell atrophy seen in females in 2-year chronic rat study, which was considered within historical background and due to aging of the rats.

In *in vitro* studies, oxamyl is not mutagenic in the Ames test (bacteria), not mutagenic in mammalian cell culture (CHO), did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, was negative for inducing DNA damage/repair, and does not cause unscheduled DNA damage in primary rat hepatocytes. These acceptable studies satisfy the pre-1991 mutagenicity guideline requirements.

Oxamyl was readily absorbed orally and eliminated in the urine (80 - 91% of the dose) and feces (< 3% of the dose). The major component present in the urine was β-glucuronide of oxime (31 - 37% of the dose), metabolite oxime (13 - 18% of the dose) and the parent oxamyl (7 - 11% of the dose). No tissue accumulation was observed. No sex differences in absorption, elimination, distribution, and metabolism of oxamyl were found. The toxicology data base provides sufficient information for selecting various toxicity endpoints and doses for assessing the risks for this chemical (page 19).

Acute RfD of 0.001 mg/kg/day was derived from the Acute Neurotoxicity Study in rats. This study was considered appropriate by the committee because neurobehavioral effects are presumed to occur after a single exposure (dose). The endpoints were selected based on ChE inhibition.

The FQPA Safety Factor Committee determined that the FQPA safety factor for protection of infants and children (as required by FQPA) be **removed (1x).**

At the August 15, 1996 meeting the HED RfD Peer Review Committee classified oxamyl as a "**Group E**" chemical based on the lack of evidence of carcinogenicity in male and female mice as well as in male and female rats. The HIARC concurred with the previous classification.

A. Acute Toxicity

Table 1 summarizes the acute toxicity data for oxamyl. Oxamyl is acutely toxic *via* the oral [rats], and inhalation [rats] routes of exposure and is not toxic by the dermal [rabbits] route of exposure in the studies required for labeling. In guinea pigs, oxamyl is not a skin sensitizer or skin irritant. Oxamyl is not an irritant to the rabbit eye. Although both primary dermal irritation and dermal sensitization studies were classified as supplementary, the information provided in these studies was sufficient for understanding the effects of oxamyl with respect to primary dermal irritation and dermal sensitization. Requiring new studies probably would not change labeling classification.

Table 1. Acute Toxicity of Oxamyl Technical

GDLN	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	00063011	LD_{50} = 3.1 mg/kg (M); 2.5 mg/kg (F)	I
81-2	Acute Dermal (Rabbit)	40606501	LD_{50} > 5000 mg/kg (M) >2000 mg/kg (F) For abraded skin 90 mg/kg produced death with 50% a.i. in water	IV
81-3	Acute Inhalation	00066902	LC50 = 0.064 mg/L (4 hr) 0.17 mg/L (M) 0.12 mg/L (F) (I hr)	II
81-4	Primary Eye Irritation	00066984	Marked pupillary constriction, conjunctival irritation, reversible by 7 days	III
81-5	Primary Skin Irritation	00066900	Minor irritation was found at the application site. Severe systemic toxicity was seen after application on the abraded skin	IV
81-6	Dermal Sensitization	00006690	4/7 animals died (25% test material) 1/5 animals died (intradermal injection) Effects seen on the test site were slight. Extreme toxicity makes dermal sensitization study relatively unimportant	Not a skin sensitizer (25% test material)

The above studies satisfy the acute toxicity data requirements (OPPTS 870.1100-870.1300, 870.2400-870.2600; formerly §81-1 through §81-6) for oxamyl.

B. Subchronic Toxicity

Available studies are adequate to satisfy subchronic testing requirements for oxamyl. There are two acceptable 21-day dermal toxicity studies in rabbits available. However, the recent, 21-day rabbit dermal toxicity study (MRID 44751201) is more appropriate for risk assessment, since cholinesterase measurements were made at the peak time of inhibition (30 - 60 minutes after removal of wrappings) and the animals were restrained from ingesting the test material throughout the study. Most of the subchronic feeding studies in rodents and non-rodents are unacceptable; however, lack of these studies does not interfere with the understanding of the toxicity of oxamyl, since acceptable chronic feeding studies are available to understand the toxicity of oxamyl. Under these circumstances, we do not need additional subchronic feeding studies in rodent or non-rodent species.

Dermal toxicity in rabbits [21-day]

(1)

In a 21-day dermal toxicity study (MRID Nos. 40827601 & 41118201; HED Doc. Nos. 006944 & 008071), oxamyl (96% a.i) was applied dermally to skin sites of male and female New Zealand White rabbits at dose levels of 0, 2.5, 50, or 250 mg/kg for 6 hours/day for 22 consecutive days. The lowest 2 groups (2.5 and 50 mg/kg/day) consisted 5 animals /sex/group; control and high dose groups, 10/sex/dose. The animals wore neck collars during the exposure (6 hours/day). It is not known whether the rabbits wore neck collars between exposures. Blood samples were collected 9 days pretreatment and 1 hours after removal of bandages following the last treatment. Hematology and clinical chemistry were done on the blood samples.

Three high dose males died during the test, but the cause of death was considered unrelated to treatment. There was a statistically significant decrease in plasma, red blood cell, and brain ChE activity in the 50 and 250 mg/kg/day male and female rabbits.

The systemic toxicity NOAEL = 250 mg/kg/day and the LOAEL was not established.

The cholinesterase inhibition NOAEL = 2.5 mg/kg/day and the LOAEL = 50 mg/kg/day, based on a statistically significant decrease in ChE activity in plasma, red blood cell and brain of males and females.

This study is classified as **Acceptable/Guideline** and satisfies the Subdivison F guideline requirement for a 21-day dermal toxicity study in rabbits (82-2).

(2)

In a 21-day dermal toxicity study (MRID 44751201), groups of 6 male and 6 female HM:(NZW)fBR rabbits were treated with oxamyl technical (96.9%, a.i.) at dermal doses of 0, 25, 40, 50 or 75 mg/kg/day, for 6 hours a day, 7 days/week. Oxamyl was moistened with water, applied to the skin and covered with an occlusive dressing during the exposure. The dosages and the peak time of effect (1 hour post unwrapping) for blood collection were based on pilot studies. The rabbits wore neck collars 24 hours a day throughout the study. No mortality was recorded, and there were no clinical signs indicative of systemic toxicity at any treatment level. No treatment-related dermal irritation was produced. There were no treatment-related effects on body weight, food consumption or food efficiency in either sex of rabbits. Significant inhibition of plasma (29%) and brain (10.7%) ChE was observed in female rabbits at 75 mg/kg/day. In addition, inhibition (24%) of red blood cell (RBC) cholinesterase in female rabbits treated with 75 mg/kg/day was noticed. In male rabbits, there were no treatment-related changes in the plasma, RBC or brain cholinesterase activities at any dose level during the study. The female plasma, RBC or brain cholinesterase activity was not statistically significantly changed at 25, 40, or 50 mg/kg/day.

Systemic toxicity was not observed in this study. The **Systemic Toxicity NOAEL = 75 mg/kg/day.**

The **Cholinesterase inhibition NOAEL = 50 mg/kg/day, and LOAEL = 75 mg/kg/day,** based on decreased plasma, red blood cell and brain ChE inhibition in female rabbits. In male rabbits, the **NOAEL = 75 mg/kg/day, and LOAEL > 75 mg/kg/day.**

The study is classified as **Acceptable/non-guideline**.

Subchronic toxicity in rats

This rat subchronic feeding study (MRID 00066911; HED Doc. Nos. 005858, 001716 & 001719) is unacceptable. However, requirement was waived since an acceptable chronic study is available.

Subchronic toxicity in mice

No subchronic feeding study in mice is available.

Subchronic toxicity in dog

This 90-day feeding study (MRID 00113398; HED Doc. Nos. 005858, 001716 & 001719) is unacceptable. This requirement was waived since a 1-year acceptable feeding study in dogs is available.

Chronic toxicity in dogs

In a 1-Year Chronic Feeding Study (MRID 41697901, 42052701 & 44737503) oxamyl (99%) was administered in diet to groups of male and female beagle dogs (5/dose) at dose levels of 0, 50, 150, or 250 ppm (equivalent to 0, 1.56, 4.60, or 8.0 mg/kg/day, for males and 0, 1.46, 4.50, or 7.84 mg/kg/day, for females, respectively). The dogs were offered the food once daily. In this study a NOAEL for male dogs was not established due to depression of cholinesterase in plasma and brain at all dose levels. Subsequently, a second one-year study (MRID 42052701) was repeated in male dogs (5/dose) at dose levels of 0, 12.5, 20, 35 or 50 ppm (equivalent to 0, 0.372, 0.577, 0.930 or 1.364 mg/kg/day). In the later study food was offered *ad libitum*.

In the first study administration of oxamyl did not produce any adverse effects in urinalysis, ophthalmological examinations, and gross pathology at any dose levels. At 50 ppm, in males, the plasma ChE was inhibited ($P < 0.05$) at 6, 9, and 12 months by 33, 34, and 32%, respectively, compared to the controls; females exhibited slight depression during the study. At this dose, only in males, brain ChE was depressed 17% compared to controls. At doses 150 ppm and above, increased incidence of clinical signs including tremors and vomiting in males and females were observed. Mean body weights/body weight gains in 250 ppm dose males and females decreased 23%/81% and 17%/49%, respectively, compared to controls and the decreases were statistically significant ($P < 0.05$). The body weight changes were accompanied by decreases in food consumption and food

efficiency. The food consumption/food efficiency of 250 ppm males decreased 11%/75% ($P < 0.05$) in comparison to the controls. In 250 ppm females food consumption and food efficiency decreased 7% and 42%, respectively, compared to control, but the decreases were not significant. Plasma cholesterol of 150 ppm and 250 ppm males and females was decreased. Histologically, 3/5 high dose males exhibited increased regenerative renal tubular epithelial alterations.

A second study (MRID 42052701) conducted to establish a NOAEL in male dogs treated with oxamyl. At 50 ppm, by study termination, the plasma, RBC and brain (cerebellum+medulla) ChE was depressed 11, 4, and 20%, respectively, compared to controls (not statistically significant). Although, marked (20%) brain ChE inhibition may not be statistically significant, it is considered biologically relevant, since tremors were observed at 150 and 250 ppm in males and at all doses in females in the previous study. At the 35 ppm dose, the plasma, RBC and brain ChE levels were depressed 18%, 5% and 2%, which appears to be the true NOAEL.

The **Systemic Toxicity NOAEL = 50 ppm (1.56 mg/kg/day for males and 1.46 mg/kg/day for females) and LOAEL = 150 ppm (4.60 mg/kg/day for males and 4.50 mg/kg/day for females),** based on decreased body weights and body weight gains.

The **Cholinesterase inhibition NOAEL = 35 ppm (0.930 mg/kg/day) for males and 50 ppm (1.56 mg/kg/day) for females, and LOAEL = 50 ppm (1.36 mg/kg/day) for males and 4.50 mg/kg/day) for females,** based on decreased brain cholinesterase levels in males and vomiting, tremors, plasma and brain ChE inhibition in females.

CLASSIFICATION: This study (MRID 41697901) in combination with the second 1-Year chronic dog study (MRID 42052701) is **Upgraded from Core-Supplementary to Acceptable/guideline** and satisfy the data requirements for a chronic toxicity study in dogs (83-1b).

Chronic toxicity/carcinogenicity in rat [feeding]

In a combined chronic toxicity/carcinogenicity study (MRID 41963101) oxamyl (97.1%, a.i.) was administered in the diet to 62 Crl:CD®BR rats/sex at dose levels of 0, 25, 50, 100 or 150 ppm (0, 0.992, 1.97, 4.19, or 6.99 mg/kg/day for males and 0, 1.32, 2.69, 6.73 or 11.1 mg/kg/day for females, respectively) for 2 years. An interim sacrifice of 10 rats/sex/dose was conducted at 12 months. Body weight, food consumption, food efficiency, hematology, clinical chemistry, urinalysis, and organ weights were recorded.

Treatment with oxamyl did not effect mortality, food consumption, food efficiency, hematology clinical chemistry, and urinalysis. At 100 and 150 ppm the incidence of hyperactivity and swollen paws/legs in males and hyperactivity and skin sores in females increased significantly ($P < 0.05$). The incidence of hyperactivity at 0, 25, 50, 100 and 150 ppm in males/females was 27%/17%, 37%/23%, 32%/20%, 52%/50% and 63%/73%, respectively. The incidence of swollen legs/paws in mid and high-dose males was 29% and 34%, respectively, compared to 11% in controls. In high-dose females the incidence of swollen paws was 23% compared to 5% in controls. High dose females exhibited

a high incidence of alopecia (56%; $P < 0.05$). Females also exhibited an increased incidence of skin sores or scabs; the incidence at 100 and 150 ppm, was 61% and 82% , respectively, compared to 39% in controls. Mean body weights and body weight gains were significantly lower in males and females at the two higher doses during the first year of study. In males at 100 and 150 ppm the mean body weight gains decreased 10% and 25% ($P < 0.05$), respectively, compared to controls. At these dose levels the female body weight gains were depressed by 27% and 37%, respectively, compared to the controls. The decreased body weights and body weight gains in males and females were considered secondary to hyperactivity since neither the food consumption nor the food efficiency was affected in these test groups. Ophthalmologic evaluations of male rats revealed 3 of 27 in the 100 ppm group and 4 of 31 in the 150 ppm group with pale ocular fundi. In females at 150 ppm, 4 of 34 rats were observed with bilateral iris atrophy. At study termination, the high-dose females exhibited ($P < 0.05$) a higher incidence of bilateral retinal photo cellular atrophy. This finding was not observed at one year sacrifice in females. At 100 and 150 ppm, in males plasma ChE levels significantly decreased 4 - 37% and 18 - 48%, respectively, during the study, compared to the controls. In females, at these dose levels, plasma ChE was inhibited 38% and 69% ($P < 0.05$), respectively, during the first month of treatment. The red blood cell and brain ChE levels in males and females were not affected at any dose level. The results did not show any treatment-related increase in tumor incidence.

Based on the results of this study (body weights, eyes lesions, hyperactivity, plasma ChE inhibition, and retinal photo receptor cell atrophy), the highest dose tested (150 ppm) appeared to be the MTD and sufficiently high to evaluate the chronic toxicity and carcinogenicity of oxamyl.

The **systemic toxicity NOAEL = 50 ppm** (1.97 mg/kg/day for males and 2.69 mg/kg/day for females) and the **LOAEL = 100 ppm** (4.19 mg/kg/day for males and 6.73 mg/kg/day for females) based on hyperactivity, swollen legs/paws, and skin sores, decreased body weights and body weight gains, increased incidence of pale ocular fundi in males and females and inhibition of plasma ChE in males.

CLASSIFICATION: The study is classified as **Acceptable/Guideline** and meets the requirements for a combined chronic toxicity/carcinogenicity study in rodent (83-5).

Chronic toxicity/carcinogenicity in mice [feeding]

In a carcinogenicity study (MRID 00076813) oxamyl (97.1%, a.i.) was administered in diet to 80 - 88 CD-1 mice/sex at dose levels of 0, 25, 50, or75/100 ppm (conversion: 0, 3.75, 7.5 or 15/11.25 mg/kg/day for males and females, respectively) for 18 months. The 100 ppm dose was reduced to 75 ppm due to mortality in the mid- and high-dose groups during the initial phase of the study; however, timing was not available. Body weight, food consumption, hematology, and organ weights were done.

Treatment with oxamyl did not effect food consumption and hematology. Body weight decrements in males persisted throughout the study period. During week 11, the body weights of the 50 and 75 ppm males decreased 5.5% ($P < 0.05$), compared to controls. In female mice, body weights decreased early in the study, however, were sporadic and were not statistically significant. Organ weights or histopathology were not remarkable. Exposure to oxamyl at 75 ppm did not increase tumor incidence.

Based on the effects of body weights in males and mortality in both sexes during the initial phase of the study, the highest dose tested (75 ppm) appeared to be sufficiently high enough for testing the carcinogenic potential of oxamyl.

The **systemic toxicity NOAEL = 25 ppm** (3.75 mg/kg/day) and the **LOAEL = 50 ppm** (7.5 mg/kg/day) based on decreased body weights in males and mortality in males and females during the initial phase of the study.

CLASSIFICATION: The study is classified as **Acceptable/Guideline** and meets the requirements for a Carcinogenicity study in rodent (83-2).

D. Developmental/Reproductive Toxicity

Available developmental toxicity and reproduction studies are adequate to satisfy guideline requirements. Oxamyl is not a development toxicant in two species and it did not affect reproductive parameters in rats.

Developmental toxicity in rats

In a developmental toxicity study (MRIDs 40859201 & 44737501) oxamyl (97.2%) was administered by gavage to groups of pregnant Charles River (CD) BR rats (25/group) at dose levels of 0, 0.2, 0.5, 0.8, and 1.5 mg/kg from gestation days 7 to 16. On day 22, the dams were sacrificed and the fetuses were removed.

There were no mortalities or treatment-related gross abnormalities reported. Maternal toxicity was observed at the 0.8 mg/kg/day dose, as decreased body weight gain (21%; $P < 0.05$), decreased food consumption (10%; $P < 0.05$) and increased incidence of tremors (4/25) associated with

cholinesterase inhibition. The decreased body weight gain and food consumption and increased incidence of tremors were dose-related. At 1.5 mg/kg/day dose the body weight gains and food consumption decreased 30% and 16% ($P < 0.05$), respectively, compared to controls. At this dose, an increased number of dams showed a statistically significant ($P < 0.05$) increase in signs of diarrhea, eye discharge, salivation, tremors, and wet legs, perineal and underbody. Treatment had no effect on the reproductive parameters and/or fetal malformations or variations. A dose-related decrease in fetal body weights was seen and decrease was statistically significant ($P < 0.05$) at doses 0.5 mg/kg and above. The fetal weights at 0.2, 0.5, 0.8, and 1.5 mg/kg, decreased 1.6%, 3.9%, 6.75% and 6.9%, respectively, compared to the controls.

The HIARC (07/15/99) noticed the apparent quantitative fetal susceptibility to oxamyl and concluded that there is no fetal susceptibility due to a decrease in maternal weight gain of 9% seen at 0.5 mg/kg/day at which decreased fetal body weights also occurred.

Under the conditions of this study, **Maternal Toxicity NOAEL = 0.5 mg/kg/day and the LOAEL = 0.8 mg/kg/day**, based on decreased body weight gains, decreased food consumption and increased incidence of tremors.

The **Developmental Toxicity NOAEL = 0.2 mg/kg/day and the LOAEL = 0.5 mg/kg/day**, based on dose-related decreases in the fetal body weight.

CLASSIFICATION: The study is classified as Acceptable/Guideline and satisfies the data requirements for developmental toxicity study (83-3) in rat.

Developmental toxicity in rabbits

In a developmental toxicity study (MRID 00063009), 17 pregnant New Zealand White rabbits per group were administered Oxamyl (97.1% a.i.; Lot No. H-10, 963-02, IND-1410-196) by gavage at doses of 0, 1, 2, or 4 mg/kg/day on gestation days (GD) 6-19, inclusive. On GD 29, all surviving does were sacrificed and all fetuses were weighed, measured for crown-rump distance, and examined for external malformation/variations. Each fetus was examined viscerally by fresh dissection and the sex determined. The heads from one-third of the fetuses were removed, fixed in Bouin's solution, and sectioned by Wilson's freehand razor technique. All carcasses were eviscerated and processed for skeletal examination.

One doe each in the low- and high-dose groups died prior to scheduled sacrifice; these deaths were attributed to gavage error. All other animals survived to terminal sacrifice. Necropsy was unremarkable. No treatment-related clinical signs of toxicity were observed in any animal in any treated group. Maternal absolute body weights and food consumption were comparable between the treated and control groups throughout the study. However, during the treatment interval (days 6 - 19), the mid- and high-dose groups had significantly ($p \leq 0.05$) reduced body weight gains as compared with the controls. Body weight gains by the mid- and high-dose groups during treatment were 39% and 33%, respectively, of the control levels. Recovery was apparent during the postdosing

interval when body weight gains by these groups were 114% and 158%, respectively, of the controls.

Therefore, the maternal toxicity LOAEL was 2 mg/kg/day based on reduced body weight gains and the maternal toxicity NOAEL is 1 mg/kg/day.

No treatment-related differences were observed between the treated and control groups for number of corpora lutea/doe, implantations/doe, preimplantation loss, fetal body weights and lengths, or fetal sex ratios. Dose-related increased resorption rates for the mid- and high-dose groups resulted in increased postimplantation losses and decreased litter sizes, but statistical significance was not reached for any parameter. For the control, low-, mid-, and high-dose groups, the mean resorptions/doe were 0.8, 0.5, 1.0, and 1.2, respectively, resulting in postimplantation losses of 10.4%, 8.7%, 15.9%, and 24.8%, respectively. The number of live fetuses/litter was 6.6, 6.6, 5.9, and 5.8. Resorptions in the mid-dose group consisted of both early (0.7/doe) and late (0.3/doe) resorptions which were not considered treatment-related. In the high-dose group only early resorptions were observed and two animals had whole litter resorption consisting of early resorptions of 1 and 7 implantation sites, respectively, are not considered treatment-related since complete resorptions in rabbits is not uncommon. Furthermore, resorptions in the high-dose group may have been a consequence of the maternal toxicity at this dose.

The number of fetuses(litters) examined in the 0, 1, 2, and 4 mg/kg/day groups was 113(17), 90(15), 89(15), and 75(13), respectively. No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetuses.

Therefore, the developmental toxicity NOAEL was 4 mg/kg/day and the developmental toxicity was not observed at the highest dose tested.

This study is classified as **Acceptable/guideline** and satisfies the requirements for a developmental toxicity study (83-3b) in rabbits. Several deficiencies were noted in the conduct of this study, however, this study was performed prior to implementation of the current guidelines.

Reproductive toxicity in rats

In a two-generation reproduction study (41660801), Crl:CD^{R}BR rats were fed oxamyl (97.1%, a.i.) in the diet at dosage levels of 0, 25, 75, or 150 ppm (approximately 0, 1.7, 5.2 or 11.6 mg/kg/day for males and 0, 2.0, 6.6 or 15.8 mg/kg/day for females, respectively). Systemic/Developmental toxicity was observed in both sexes and generations at 75 ppm and above as significantly decreased food consumption (F_0 males and females 14.6 - 15.7%, F_1 males and females 9.9%- 16.8%), body weight (F_0 males and females 5 - 9%, F_1 males and females 7 - 20%) and body weight gain (F_0 males and females 14.6 - 20.7%, F_1 males and females 13 - 13.7%). In addition, at 150 ppm, a significantly increased incidence of clinical signs (hyperactivity, skin sores and alopecia) was observed.

Based on these results, the **NOAEL for systemic/developmental toxicity was 25 ppm** (approximately 1.7 and 2.0 mg/kg/day for males and females, respectively); **the LOAEL was 75 ppm**

(approximately 5.2 and 6.6 mg/kg/day for males and females, respectively).

Offspring toxicity was observed at 75 ppm and above in both generations as significantly decreased body weight during lactation in both generations (2 - 7.6%). In addition, at 150 ppm, the number of live pups per litter and the viability index decreased 15.7 - 16.4% and 21 - 43%, respectively. Based on these results, **the NOAEL for offspring toxicity was 75 ppm** (approximately 5.2 and 6.6 mg/kg/day for males and females, respectively); **the LOAEL was 150 ppm** (approximately 11.6 and 15.8 mg/kg/day for males and females, respectively).

CLASSIFICATION: The study is **Acceptable/Guideline** and satisfies the guideline requirements (83-4) for a Reproduction Toxicity Study in Rats.

E. Mutagenicity

There are 12 mutagenicity studies available, and several of these studies are classified as unacceptable. The acceptable studies together satisfy the pre-1991 mutagenicity initial testing battery guidelines. These genetic toxicology studies indicate that oxamyl does not present a mutagenicity concern at this time. Following are the acceptable studies:

GENE MUTATIONS

1) *Salmonella typhimurium* reverse gene mutation assay (MRID 40606509; HED Doc. # 006891& 007077): The test is in *S. typhimurium* strains TA1535, TA1537, TA98 and TA100 at doses ranging from 50 to 10,000 μg/plate with or without S9 activation. The test is negative in all strains and concentrations. This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

2) Chinese hamster ovary (CHO) HGPRT forward gene mutation assay (MRID 40606510; HED Doc. # 006891& 007077): The test is negative in independently performed trials up to concentrations causing < 80% decrease in cell viability (1200 μM -S9; 700 μM +S9). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

CHROMOSOMAL ABERRATIONS

3) In vitro CHO cell chromosome aberration Assay (MRID 40606507; HED Doc. # 006891& 007077): The test was negative up to cytotoxic concentrations ($\leq$ 70 μg/mL -S9; 700 μg/mL +S9). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

OTHER MUTAGENIC MECHANISMS

4) DNA damage/repair in *Bacillus subtilis* rec assay (MRID 00049594; HED Doc. # 005858): The test was negative up to the highest dose tested (2000 μg/disc -S9). This study is classified as

acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

5) In vitro unscheduled DNA syntheses in primary rat hepatocytes (MRID 40606508 & 41096001; HED Doc. # 006891& 007595): The test is negative up to cytotoxic concentrations (≤ 5 nM). This study is classified as acceptable/guideline study and satisfies the requirements for FIFRA Test Guideline 84-2.

F. Metabolism

Available metabolism data are adequate to satisfy the guideline requirements. With oral administration, oxamyl was readily absorbed and eliminated in the urine (80 - 91% of the dose) and feces (< 3% of the dose). The major component present in the urine was β-glucuronide of oxime (31 - 37% of the dose), followed by the metabolite oxime (13 - 18% of the dose) and the parent oxamyl (7 - 11% of the dose). No tissue accumulation was observed.

1)

In a rat metabolism study (MRID 41520801; HED Doc. No. 010035 & 010017), SD rats (5 animals/sex/group) received a single oral dose of ^{14}C-oxamyl (1 mg/kg) by gavage. Approximately 80% of the administered radioactivity was eliminated in the urine after 24 hours of dosing, and approximately 91% of the dose was eliminated in the urine by 168 hours. Less than 3% of the dose was found in the feces, and approximately 1% of the dose was found in the carcass. Except for muscle and skin, less than 1% of the dose was found in any tissue examined. The data indicated that oxamyl was readily absorbed with oral administration and rapidly metabolized and eliminated in the urine. There was no sex difference in the pattern of elimination, and there was essentially no sequestration of oxamyl or its metabolites in any tissue examined.

Oxamyl is hydrolyzed to an oxime, which is mainly found in the urine; (approximately 13% of the administered dose in male and 18% of the administered dose in females) and which had lower toxicity than oxamyl. The oxime is conjugated with glucuronic acid to form the major metabolite.

The results of this study provide sufficient information for the understanding of metabolism of oxamyl. The is classified as **Acceptable/Guideline** and meets the requirements for a metabolism study (85-1). Since oxamyl is acutely toxic and demonstrated no carcinogenic potential, an additional metabolic study is not required at this time.

G. Neurotoxicity

Available neurotoxicity studies were adequate to satisfy the guideline requirements.

Acute neurotoxicity in hens

In a invalid acute delayed neurotoxicity study (MRID 00066893; HED doc. No. 001716 & 005858)

in hens, clinical signs of depression, lethargy, ataxia, ruffled feathers, incoordination, and slight respiratory difficulty were seen in treated hens. These symptoms disappeared 12 hours after dosing. No compound related histological changes were seen, and no deaths occurred in the treated hens. This study is classified as unacceptable for lack of individual bird and histopathology data. This requirement is waived since acute and subchronic rat neurotoxicity studies are available which adequately demonstrate the neurotoxicity potential of oxamyl

Acute neurotoxicity in rats

In an acute oral neurotoxicity study (MRID Nos: 44254401 & 44420301 & 44740701), single gavage doses of oxamyl (98.3% a.i.) in deionized water were administered to groups of Crl:CD rats (42/sex/dose). Males received 0, 0.1, 1.0, or 2.0 mg/kg and females received 0, 0.1, 0.75, or 1.5 mg/kg. Twelve rats/group were designated as neurotoxicity subgroup animals. All twelve of these rats/group were used for Functional Observational Battery (FOB) and Motor Activity (MA) assessments on days 1, 8, and 15. Body weight and clinical signs were also recorded for these animals. Six of the rats/group were euthanized for *in situ* perfusion. Thirty rats/group were designated as the clinical pathology group and were utilized for blood and brain collection for evaluation of cholinesterase levels.

One high-dose male died on day 1. High-dose males had significantly ($p<0.05$) decreased mean body weight gain for days 1-2. Similarly, mid-dose males and high-dose females also exhibited lower (n.s.) body weight gains. Decreased food consumption (n.s.) was also observed in mid- and high-dose males.

Statistically ($p<0.05$) and biologically significant dose related decreases in blood and brain cholinesterase activity were observed in mid- and high-dose males and females on day 1 at the peak time of effect (30 - 60 minutes post-dosing). Mean decreases were generally $\geq$40%. By day 2, decreases in cholinesterase activity were no longer biologically significant. No toxicologically significant decreases in cholinesterase activity were observed in any animals after day 1 or in low-dose males and females at any time point.

Clinical signs and FOB effects, consistent with decreased cholinesterase activity, were observed 30-60 minutes post-exposure in the mid- and high-dose males and females. Observations included soiled fur, lacrimation, salivation, slow righting reflex, abnormal gait, tremors, impaired locomotion, no response to tail pinch, increased limb splay, incoordination, labored breathing, and decreased forelimb and hindlimb grip strength. Other effects, included abnormal posture, palpebral closure, docile behavior, and decreased motor activity. No treatment-related clinical signs or FOB effects were observed in low-dose animals or after day 1. Therefore, **the RBC, plasma and brain ChE inhibition NOAEL = 0.1 mg/kg/day for males and females and LOAEL = 1.0 mg/kg/day in males and 0.75 mg/kg/day in females.**

No treatment-related gross effects or histopathology were observed.

Under the conditions of this study, **the systemic/neurotoxicity LOAEL is 1.0 mg/kg for male rats and 0.75 mg/kg for female rats based on clinical signs, FOB effects, and decreased blood and brain cholinesterase activity. The NOAEL** is 0.1 mg/kg.

This acute oral neurotoxicity study is classified **Acceptable/Guideline**. This study does satisfy the guideline requirement for an acute oral neurotoxicity study (81-8) in rats.

Subchronic neurotoxicity in rats

In a subchronic oral neurotoxicity study (MRID 44504901), 42 Crl:CD^{R}(SD)BR rats/sex/exposure group were administered Oxamyl Technical (purity, 98.3%) at concentrations of 0, 10, 30, or 250 ppm (equivalent to 0, 0.564, 2.10, or 14.9 mg/kg/day for male rats and 0, 0.679, 2.40, or 19.9 mg/kg/day for female rats, respectively) in the diet. The 30 and 250 ppm concentrations were reduced from 100 and 300 ppm, respectively, on day 7 of administration due to toxic effects including tremors and weight loss. Twelve rats/sex/exposure group were assigned to the neurotoxicity group and underwent functional observational battery (FOB) and motor activity (MA) testing prior to dietary administration and during weeks 4, 8, and 13. Ten rats/sex/exposure group were sacrificed on days 27 and 55 and at termination of the study for cholinesterase activity determinations. Six rats/sex/exposure group (from the neurotoxicity group) were perfused for neuropathology at study termination.

All animals survived to scheduled termination. At the end of 90 days, body weights of male and female rats receiving 250 ppm in the diet were significantly depressed by 24% and 10%, respectively ($p<0.05$). Decreases in body weights correlated with decreased food consumption in males and decreased food efficiency in both sexes. Exposure-related clinical signs (tremors, abnormal gait or mobility, hunched-over posture, exophthalmus, ptosis, hyperactivity, piloerection, colored discharge from the eyes, hyperactivity and lacrimation) were present in one or both sexes administered 250 ppm in the diet but not in animals administered 30 or 10 ppm. During the FOB, significant changes in incidences of ptosis, piloerection, abnormal gait, pupillary response to light, and hindlimb grip strength were observed in either male and/or female rats administered 250 ppm. At the end of the study, the mean plasma, RBC and brain (cortical) ChE levels were decreased by 24, 48 and 40%, respectively in males and 60, 55, and 51%, respectively in females, compared to controls. Decreases in brain and blood cholinesterase activity correlated with the presence of clinical signs and changes in FOB parameters in the 250 ppm group. Generally, the magnitude of ChE inhibition was greater in females than males; and there was no cumulative effect with time. Motor activity was not significantly affected at any concentration. No oxamyl-related neuropathological changes were observed in any exposure group.

Under the conditions of this study, the **Systemic Toxicity LOAEL is 250 ppm (14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively), based on decreases in body weights and food efficiency of both sexes. The NOAEL is 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively).**

The LOAEL for neurobehavioral effects is 250 ppm (14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively) based on decreases in plasma, RBC and brain ChE activity, clinical signs consistent with cholinesterase inhibition, and changes in incidences of FOB parameters such as increases in ptosis, piloerection, and abnormal gait and decreases in pupillary response to light and hindlimb grip strength. The NOAEL is 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively).

The LOAEL for ChEI was based on decreased plasma, RBC and brain ChE activity. The ChE LOAEL = 250 ppm **(14.9 mg/kg/day and 19.9 mg/kg/day for male and female rats, respectively) and NOAEL = 30 ppm (2.10 mg/kg/day and 2.40 mg/kg/day for male and female rats, respectively).**

This study is classified **acceptable** and satisfies the guideline requirement for a subchronic oral neurotoxicity study (82-7) in rats.

II. Uncertainty Factor/FQPA Considerations

The following evaluation of the chemical oxamyl is provided to address FQPA considerations on the sensitivity of infants and children.

The application of a FQPA Safety Factor to ensure the protection of infants and children from exposure to oxamyl, as required by FQPA, was determined by the HED FQPA Safety Factor Assessment Review Committee [see below]. The HIARC recommended to the FQPA Safety Factor Committee that the FQPA 10X Safety Factor be removed because there was no increased susceptibility to fetuses following *in utero* exposure in the developmental toxicity study in rats and rabbits and in a 2-generation reproduction toxicity study in rats. Oxamyl was presented to the HED FQPA Safety Factor Committee on August 30, 1999.

The FQPA Safety Factor Committee determined that the 10x FQPA safety factor should be removed, based on the following:

(1) The toxicology data base is complete for FQPA assessment;

(2) The HIARC concluded that the toxicity data provide no indication of increased susceptibility of young rats or rabbits to oxamyl;

(3) The HIARC determined that a developmental neurotoxicity study is not required;

(4) The exposure assessments will not underestimate the potential dietary (food and drinking water) exposures for infants and children from the use of oxamyl; and

(5) There are currently no residential (non-occupational) uses of oxamyl.

A copy of the FQPA Safety Factor Committee Report, dated September 13, 1999 [HED Document No. 013737] is appended.

III. Toxicity End-Point Selection

On June 8 and August 15, 1999, the Hazard Identification Assessment Review Committee [HIARC] evaluated the entire toxicological database on oxamyl and selected the relevant toxicity endpoints, taking into consideration the use patterns and exposure information on this chemical. The selected toxicological endpoints and the doses for risk assessment are summarized in Table 2 and additional relevant details for each endpoint are presented.

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13+)	Acute Neurotoxicity NOAEL=0.1	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat
	Acute RfD = 0.001 mg/kg		
Acute Dietary (General Population including Infants & Children)	Acute Neurotoxicity NOAEL=0.1	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat
	Acute RfD = 0.001 mg/kg		
Chronic Dietary	NOAEL=0.1	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat
	Chronic RfD = 0.001 mg/kg/day		
Short- Term (Dermal)	Dermal NOAEL=50	LOAEL = 75 mg/kg/day is based on plasma, red blood cell and brain ChEI in females	21-Day Dermal Toxicity - Rabbit
Intermediate- Term (Dermal)	Dermal NOAEL=50	LOAEL = 75 mg/kg/day is based on plasma, red blood cell and brain ChEI in females	21-Day Dermal Toxicity - Rabbit
Long-Term (Dermal)	Based on the use pattern (applied using groundboom, aerial, airblast, chemigation, soil injection, handgun sprayer, and bulb dip equipment at the rate of 0.25 to 8 lb ai/acre, may be applied at weekly intervals up to a maximum of 6 applications/crop cycle), this risk assessment is not required.		
Inhalation (Short & Intermediate) [a]	Acute Neurotoxicity NOAEL=0.1	LOAEL = 0.75 mg/kg/day is based on clinical signs, and decreased plasma, red cell and brain cholinesterase inhibition in females	Acute Neurotoxicity - Rat
Inhalation (Long-Term) [a]	Based on the use pattern (applied using groundboom, aerial, airblast, chemigation, soil injection, handgun sprayer, and bulb dip equipment at the rate of 0.25 to 8 lb ai/acre, may be applied at weekly intervals up to a maximum of 6 applications/crop cycle), this risk assessment is not required.		

a = Appropriate route-to-route extrapolation should be performed for these risk assessments. Exposure values using absorption factors of (%) for dermal and 100% for inhalation (default value) should be converted to equivalent oral doses and compared to the oral NOAEL.

A. DERMAL ABSORPTION FACTOR

A dermal absorption factor is not required since a dermal NOAEL was selected for Short- and Intermediate-Term dermal exposure risk assessment; the use pattern does not indicate long term dermal exposure potential. In addition, there is no carcinogenicity risk associated with oxamyl. Therefore, Long-Term dermal risk assessment is not required (HIARC Report dated August 31, 1999; HED Doc. No. 013711).

IV. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for food-use chemical by 40 CFR Part.

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